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ECHO: HIV ASSOCIATED NEUROCOGNITIVE DISORDERS AND DEPRESSION IN LONG TERM HIV SURVIVORS

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00:00
Hi everybody. So I have found that, particularly over the course of the pandemic, a lot of my older patients have had issues of isolation, depression, with compounding cognitive issues. This led me kind of back into the research around HIV dementia, and aging and HIV, and cognition. And that has led me to, unfortunately, a lot of mixed data, which I kind of have tried to compile here to kind of give a little bit clearer picture on depression and cognition in long term HIV survivors, from what we know right now.

00:56
So I think most folks here who work with HIV positive patients have heard of HIV Associated Neurocognitive Disorder, used to be called HIV Dementia, we now call this cluster of disorders HAND. And then we'll also discuss some epidemiology of HAND and the changes that have happened with the epidemiology of HAND in the last 20 or 30 years. And also we'll review the difference between the symptom of apathy, which can be a cognitive symptom, and a traditional depressive disorder. And maybe how to distinguish between those two, and maybe if that's even that useful distinction at all.

01:36
But to go over HAND, or HIV Associated Neurocognitive Disorders, very early on it was found that people who live with HIV have some type of cognitive impairment. Since this had really started being measured in the early 1990s, anywhere from about a third to about a half of people of living with HIV have some sort of cognitive impairment. And that's controlling for other factors like mental illness, HCV infection, and other neurological disorders. In fact, in the 1980s and early 1990s, it was a lot of these really dramatic cognitive dysfunctions and behavioral dysfunctions for what brought psychiatry in pretty close contact with infectious disease, to manage these patients on an inpatient and outpatient basis. Sort of started the revolution in collaborative care in psychiatry in the 1980s. But these cognitive deficits are often under diagnosed, because many of the impairments these days are quite mild and only discoverable through intensive neuropsychological batteries, which are rarely covered by insurance. And there's also a lot of debate over what is the utility of these neurocognitive batteries, if the patient doesn't experience any dysfunction. We'll kind of get into that in a little bit. But these cognitive deficits can dramatically affect people's quality of life, as one can imagine, in terms of ADLs. As well as affect medication adherence, and just the course of the disease overall.

03:14
And as the demographics of HIV have changed from the 1990s, due to ART, the presentation of HAND has dramatically changed. And to kind of give an overview before we get into the epidemiology of what we're talking about when we talk about the cluster of HAND diagnoses, so the most mild form is Asymptomatic Neurocognitive Impairment or ANI. And ANI is defined as having one standard deviation below the mean in any sort of cognitive battery, and there's all these different types of cognitive batteries, in two domains or more. But this also comes with no functional impairment experienced by the patient in ADLs. Often complete unawareness of it by

the patient, they are able to compensate for this using other cognitive reserve. Minor Neurocognitive Deficit, or MND, sometimes it's called minor motor neuro deficit, is one standard deviation below the mean in two cognitive domains. So the same as ANI, but with impairment in ADLs. So either basic or instrumental activities of daily living. Basic activities being things like washing yourself, getting food. Instrumental being things like managing your finances, making appointments, etc., being able to work. And HIV Associated Dementia, or HAD, is two standard deviations below the mean, so a significantly greater impairment in two or more cognitive domains with severe or marked impairment in ADLs.

04:52
And these are sort of the research clusters that we use and how we describe it in most research settings. And when you translate that over to the DSM and ICD codes, ANI actually has a no diagnosis code, and you can't really bill for it, it's very difficult to kind of work with ANI, and in many cases requires no treatment anyway. And then Minor Neurocognitive Disorder becomes minor neurocognitive disorder. And then HIV Associated Dementia is a major neurocognitive disorder.

05:29
And these are two graphs, please excuse my very poor graphic design skills here. I hope this is somewhat readable. But as you can see from the top graph, measuring the age of HIV positive people in San Francisco from 1996 to 2015, you can see the percentage of people over 50 years old has greatly increased over that time. And HIV/AIDS is no longer a disease of primarily young people, because people are living with it much longer than they used to. And of course, I think this probably has something to do with the demographics of San Francisco changing overall. But I was able to find two studies that were done by the same researcher, one in 1995 and one in 2010, using very similar means looking at measuring HAND in a group of similar patients. And so sort of this larger bar, and you can see that the prevalence of HAND has not changed particularly much, you know, maybe a couple percentage points overall in the course of 15 years there, with none being the sort of large orange bar on the right. The black bar is Asymptomatic Neurocognitive Impairment, the gray bar Minor Neurocognitive Disorder, and then this sort of second orange bar is, small orange bar, is HIV Associated Dementia. So, you can see that the rates have changed a lot in where the people fall in those categories. So Asymptomatic Neurocognitive Disorder has increased and mostly HIV Associated Dementia has greatly decreased. And that has a lot to do with ART, and the initiation of ART, and being able to suppress viral loads is much easier than it was in the 1990s.

07:34
So in pre-ART, HIV Associated Dementia was a subcortical dementia, so affecting primarily the white matter. And another typical subcortical dementia is Parkinson's Dementia, so you kind of see that they're somewhat similar. The first signs are usually worsening attention and concentration and psychomotor slowing, as well as a lot of motor deficits. So sometimes the earliest signs of HIV Dementia were difficulty with gait, so trouble running, trouble typing, and fine motor skills. And there were a lot of behavior components. So alterations in sleep, either like terrible insomnia or altered sleep wake cycles. Apathy, so not being able to enjoy anything, and we'll kind of get into a little bit more what apathy is technically later on. Depression,

psychosis, and then AIDS mania, which was sort of a famous psychiatric complication that, luckily, is quite rare these days. Was almost like a delirium mixed with mania, very difficult to treat and often fatal. Memory was usually a lagging symptom and was often sometimes not affected at all. And the course was degenerative and extremely quick, so death often within a year of diagnosis.

08:50
Post-ART HAND presents largely as a cortical dementia, and the most common cortical dementia is Alzheimer's. So you can think of it kind of a parallel there. Memory and executive dysfunction are usually the most prominent symptoms, as they are in Alzheimer's disease. There are fewer motor and behavioral components. And the course is much less degenerative, it's often stable or say wobbly. So people move between Asymptomatic Neurological Impairment and Minor, and they kind of go up and down between the two. And that seems to have not a lot of relation to CD4 count or viral load, assuming that viral load is relatively suppressed. And it can be kind of unpredictable and again, get better and get worse over the course of years. And it's a lot more easily confounded with other neurological disorders like Alzheimer's or other cognitive issues in aging populations, like vascular dementia or say Parkinson's disease. And that's because the disease process is very different when someone has virally suppressed HIV versus when HIV is not virally suppressed.

10:07
And this is a great diagram from that study below, showing that HIV pretty much infects macrophages and gets into the brain through the blood brain barrier in these macrophages. And then goes on to infect other cells in the brain, like microglia and astroglia, and causes neurotoxicity to neurons. And in uncontrolled HIV, HIV replicates sort of wildly in the CNS, you get this terrible neuroinflammatory responses with HIV related encephalitis. You get these multi-nucleated giant cells that cause you know, catastrophic harm to the neurons, and astrogliosis, myelin loss, and neuronal loss, and synaptic damage. And that leads to further opportunistic infections and progression to AIDS and AIDS-related CNS infections and pathology, like toxoplasmosis and lymphoma.

11:05
But when someone is on ART and their HIV is suppressed largely in the CNS, it becomes a more chronic problem. So you get this sort of microgliosis, this mild astrogliosis, some myelin loss over the course of years, and then sort of protein aggregates similar that you would get in something like Alzheimer's disease. And it causes sort of this much slower progressive disease, rather than sort of a rapidly progressive degenerative disease. And then you also have these other comorbidities that come into effect, things like aging, drug abuse, cancers not related to HIV, cardiovascular disease, and Hepatitis C, which can further kind of increase the oxidative stress on the brain and worsen these cognitive deficits.

12:01
So the mechanisms are still rather poorly understood for these like long term cognitive deficits. It's postulated that certain HIV proteins, such as gp120, tat, and nef, activate neuroinflammatory and apoptotic pathways, which leads this inflammation over the long term. gp120 is probably the

best studied of these. And when combined with normal aging, it leads to worse dysfunction in older HIV positive individuals. So in this case, older than 50 in this one study. And this was a study of about 200 people about half HIV positive and half HIV negative, about 60% were male, largely Caucasian, and sort of middle income, most of them. The older HIV positive population was much more likely to have deficits in instrumental activities of daily living, which is the graph on the right, and that's things like ability to manage your finances, make appointments, and sort of have these higher cognitive functions that are required for living independently, And also dysfunctions in basic activities of daily living, like being able to feed yourself, to cook, to wash, and to communicate. And we still see some deficits in younger folks with HIV, in this case people younger than 50. And the average, I think, in this study was around 35. It just is further compounded by aging, in ways that we don't fully, I think, understand yet.

13:38
And compounding this, people with HIV are at higher risk for depression, and as are the elderly who have medical problems. So people living with HIV, broadly, are two to three more times likely to suffer with a depressive disorder over the course of their lifetime than the general population. And the most are widely cited, and I think that best demographic study, there's about a 39% lifetime prevalence versus anywhere from a 10 to 20% in the general population. This can certainly, as we all know, impact quality of life, medication adherence. And, in that way, impacts the course of HIV. And is often compounded by things like the effects of HIV, like fatigue. And ART, including things like somatic symptoms, nausea, and sedation that can happen from these medications. Luckily, a lot fewer psychiatric symptoms than there had been 10 years ago. And the prevalence of depression in older adults, and in this study that meant older than 65, is higher in those with medical illness, functional impairment, history of substance use disorder, and barriers to accessing medical care. Which is, you know, pretty much all of my patients that I see. And this makes HIV elders a particularly vulnerable population to depression.

14:59
And so depression and cognitive disorders can look somewhat similar, because of this sort of cognitive construct that we call apathy, which is slightly different from depression. So, apathy is a reduced self-initiated cognitive and emotional behavioral activity, so sort of the inability to start things. So that includes social interactions, inability to attend to your ADLs, an inability to engage in pleasurable activities as well. And in some cases, inability to, you know, even make medical appointments, or get out of the house. In extreme cases, this can lead to things like catatonia. But that's, I think, kind of out of the scope of what we're talking about today. Depression, as we talk about it in the DSM anyway, is more of a constellation of symptoms. It includes affective components like sadness, anger, despair, anhedonia which is the inability to feel positive emotions, and hopelessness and guilt. As well as somatic components like changes to sleep, appetite, energy level. And physical symptoms, particularly in the elderly, things like nausea, headaches, muscle aches. And then cognitive components, which is also more common in the elderly, things like deficits in concentration, feeling slow, and memory impairment. And I think we'll look at the next study that shows that depression really affects just about every cognitive domain. And then there's also the, you know, can someone have both? Absolutely. Cognitive impairment definitely increases one's risk for developing depression, especially mild cognitive impairment where someone is able to sort of witness their own deficits.

16:57
So a team in Rhode Island looked to sort of see if there was, first of all, any utility in apathy as a construct, in determining if we can look at apathy, can we determine if someone has more like a depression or cognitive disorder? And also to see if apathy was a predictor of cognitive decline independent of depressive symptoms. So they looked at about 120 HIV positive individuals, about 60% male, about half white, and an average age of 45 with a standard deviation of about 10 years. And then they went through a number of inventories with these folks, including a substance use inventory, a depression inventory, an apathy inventory which is part of something called the frontal systems behavioral scale, which is sort of their measure of apathy in this one. That's another problem with sort of measuring apathy is people use different scales. And then cognitive batteries. And what they found was that depression, much more than apathy, predicted cognitive deficit. Apathy didn't really have a lot of predictive factors in terms of HIV related dementias. And depression wound up lowering just about every cognitive domain, including things like executive function, memory, concentration, and learning, and sort of like plasticity of the brain, so the ability to like learn new information. More than even apathy did. History of alcohol use was predictive of depression, and then age and the history of cocaine use were predictive of apathy.

18:45
So as with many things in psychiatry, is this apathy versus depression a useful construct? Answer is maybe. And it's something to keep in mind for patients who maybe don't have the full cluster of symptoms of depression, but you're noticing that something is off with them, or they're not making their appointments regularly, they've had a change in their medication adherence. Consider something like HIV Associated Neurocognitive Disorders, and perhaps a referral or a screen.

19:16
So how does one screen for HAND in this sort of new era of HAND? So first of all, looking at a patient's risk factors can be helpful. So the biggest one is unsuppressed viral load. If the person is still in active HIV, then getting that under control is really important. And things like age so you know, just absolute age, how old someone is. CD4 nadir/AIDS diagnosis in the past, duration of time living with HIV, a history of substance use of any kind, a history of HIV related CNS disease like lymphoma or toxoplasmosis, and Hepatitis C, all increased risk for HAND. There are unfortunately no longer any good screening tools for HAND. The International HIV Dementia Scale was developed in like the late 80s and early 90s to screen for that other type of dementia, the rapidly progressive dementia, and is no longer sensitive or specific for HAND. And neither is the Folstein Mini Mental and neither really is the MOCA. So what do I use? I use the MOCA because the MOCA assesses a lot of different cognitive domains, as well as the HIV Dementia Scale. So I usually kind of use them together, they have some things that overlap, but I think particularly the psychomotor speed testing on the HIV Dementia Scale I found helpful. And I also have in my office something called a grooved pegboard test. So a grooved pegboard is this little guy right here, there are these little pegs that look kind of like keys. You can see in the holes there, there are sort of circles, and they each have a slot. So with one hand, you have to grab all of the pegs and move them into the slots and sort of manipulate them and get them all

done. So with the right hand and the left hand. And this has had good utility in showing sort of minor motor deficits, as well as psychomotor speed. So those combined, I kind of get a pretty good sense of whether or not someone has HAND or perhaps something else if they're coming in with neurocognitive deficits and no other confounding factors, like depression or substance use.

21:41
Referring to psychiatry or psychology, if possible. And then to really get a true diagnosis though, you need to refer the person to neuropsychological testing, if the patient has functional deficits. And we do have a neuropsychological testing department here, but it can be difficult to get appointments. And then of course getting the person if they have functional deficits to attend those appointments also can be really difficult. So getting care coordination involved, if that's available at your institution.

22:09
And then screening for depression at the same time. So the PHQ, our favorite screening tool, is quite sensitive for depression. So it definitely catches most people who have a depressive disorder. But you know, always keep in mind the PHQ doesn't necessarily measure severity or functionality terribly well. And then referring to psychiatry as needed to treat depression, because with depression treated often cognitive deficits get much better. It's generally not a good idea to screen for HAND if someone isn't in a current depressive episode. So if you're noticing that they're feeling much more depressed or they have untreated depression, or an untreated substance use disorder, managing that prior to doing the HAND screening will give you a much more accurate result. Otherwise things can get rather easily confounded, especially because the HAND screening is not that great.

23:06
And then, you know, treatment for HAND if it is uncovered, it is unfortunately rather limited. So again, controlling HIV, the most important part. Going on ART for one year improved functioning in attention, processing speed, executive dysfunction, and correlated most closely with rising CD4 levels. So really, if someone is developing cognitive symptoms, that's the thing to do. Reducing or getting someone abstinent from substances, including alcohol, can really improve cognitive function in the long term. And then treating co-occurring medical and mental illnesses like Hepatitis C, depression, PTSD, can also improve cognitive function. And then also ensuring that you've ruled out other treatable diseases like Alzheimer's disease, drug use, or anything else that you can also treat. And there have been many, many trials for different medications. This is sort of a very brief overview. NMDA antagonists like nameda, cholinesterase inhibitors like Aricept, antidepressants, valproate, and stimulants, have all shown basically a negative or no effect when it comes to treating HIV related cognitive deficits. Stimulants, however, are something that I do occasionally use in people who have HAND, partly because they help a lot with fatigue, which can be a presenting symptom, as well as mood in some cases. There is no evidence right now, and this is something that was tried years ago, of ART regimens with more CNS penetration preventing HAND from developing. That just hasn't been seen, or at least not enough to recommend doing that proactively. And then of course addressing psychosocial issues, so what the pandemic has shown everyone, human contact is super important. And

particularly for our HIV positive elders, there's often a isolation which can worsen cognitive symptoms, worsen depression. And then also, when it comes to treating depression in HIV positive elders, medication management. At least with medication management, the most important thing is to start low and go slow with antidepressants. So I usually start at half the dose or sometimes even less when I'm starting on these new medications, partly because the chronic effects of HIV can impact medication side effects. This is particularly true of neuroleptic medications, things like anti psychotic medications, but can also be true like of antidepressants, particularly ones that effects like dopamine and norepinephrine, like duloxetine, Wellbutrin, etc.

26:02
So make sure you're considering renal and hepatic dosing, and drug-drug and drug-disease interactions become more important as polypharmacy increases. With psychiatric medications, you're really going to look at things like anticholinergic effects, and alpha antagonism effects, making sure their blood pressure isn't getting too low, they're not at risk for falls, and they're not at risk for things like delirium or urinary retention. And again, with antidepressants, particularly paroxetine, TCAs, and antipsychotic medications, are going to be the biggest culprits there. And avoid neuroleptics and benzodiazepines if possible. You know, of course, some people who have chronic psychotic diseases or bipolar disorder need to be on neuroleptic medications like anti psychotics on the long term. But if you're treating someone who has a behavioral issue related to dementia, try to avoid anti psychotics as much as possible because they lead to an increase in all cause mortality when given on a daily basis. If there's someone who can tolerate PRN, that's a potential solution there too. And then often people who do have these chronic psychiatric issues, reducing the doses of the neuroleptics as they grow older often gives you the same effect with reduced side effects. And the side effects, that I've noticed anyway in my patients who have gotten older, are related to motor and neurological side effects. So increased tremor or bradykinesia, cog wheeling, and rigidity. And even pulling back a lot on the Risperdal or Haldol has helped these folks out a lot without increasing their risk for psychiatric symptom relapse. Benzodiazepines, always use with caution, and particularly in elderly it can increase risk for delirium, cognitive issues, as well as falls. And this increases rather dramatically over the age of 65.

28:05
And kind of the last slide is sort of a shout out to SAGE, which is an advocacy group for queer elders. And many of our patients, certainly in my clinic, are queer folks. And LGBT elders are two times as likely to live alone, they're four times as likely to not have children, and often don't have social support into aging. And here on the news, you know, a lot of tragedies about people either being removed from their homes or having to go into nursing homes, because they don't have that support that many other people do. And SAGE in New York City offers community based services, particularly things like groups, events, low cost meals, home visits, and then bridges to medical care or other resources. And I think, sorry, I didn't put even the number there. I'll send that out later. But they have a hotline number that patients can call and get connected into their coordination of services relatively easy. It's a pretty low bar. And I've referred a number of my clients over the course of the pandemic to SAGE who've been really great about sort of making them feel like part of a community again, when they've been really so isolated by the pandemic.

29:29
And here are some of the references, those are the references for the pie charts I had are on the slides. But if anyone has any questions or cases that they've had with patients with neurocognitive disorders, happy to take any questions.

[End]